Report of the Peer Consultation Meeting on Methyl Ethyl Ketone

Submission by the
VCCEP Task Group of the
American Chemistry Council Ketones Panel
for the
Voluntary Children's Chemical Evaluation Program
(VCCEP)

February 19, 2004
Cincinnati, Ohio

Peer Consultation Organized by
Toxicology Excellence for Risk Assessment (*TERA*)
(http://www.tera.org/peer/vccep/MEK/MEKwelcome.html)

April 19, 2004

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Executive Summary

A panel of scientists with expertise in toxicity testing, risk assessment, exposure assessment, and children's health met on February 19, 2004, to conduct a peer consultation of a submission on methyl ethyl ketone (MEK). The American Chemistry Council Ketones Panel prepared the submission for the Voluntary Children's Chemical Evaluation Program (VCCEP). The purpose of the meeting was to provide a science-based forum to discuss whether the existing data are adequate to characterize the risks of MEK to children, and, if not, to identify data needs.

The sponsors provided the panel with brief presentations summarizing the submission's assessments of hazard, exposure, risk, and data needs. They noted that studies conducted on MEK directly, or on its immediate precursor, secondary butyl alcohol (sBA), fulfill the hazard requirements listed in the VCCEP Tiers 1 and 2. The available studies included a rat oral 2-generation reproduction study and a mouse inhalation developmental toxicity study, which were used by U.S. EPA to derive Reference Dose (RfD) and Reference Concentration (RfC) values. The critical effects in these studies were decreased pup weights and skeletal variations, respectively. The sponsors explained that MEK is a mammalian metabolite, is present in all food groups, and is produced by plants and microorganisms. MEK's primary use is industrial, but it also is an ingredient in consumer products. On a chronic basis, food ingestion is the main exposure pathway for children, including the nursing infants of non-occupationally exposed mothers. On a short-term basis, inhalation exposure from using consumer products may exceed the oral exposure from foods. The risk assessment for chronic exposure compared aggregated annualized exposures for all age groups in the general population to the RfC and RfD values. These comparisons resulted in a margin of safety (MOS) of 17 for the highest exposed active group and a MOS of 22 for the highest exposed passive group. Comparison of acute exposure data to the sensory irritation threshold and to acute exposure benchmarks based on developmental effects resulted in MOS values greater than 1 for all age groups. The risk assessment for nursing infants of occupationally exposed mothers compared a worst-case exposure estimate to the RfD, resulting in a MOS of 4. The sponsors concluded that the quantitative risk characterization demonstrated that children's exposure to MEK poses negligible adverse health risks because the MOS values for all target populations were greater than 1. On this basis, they concluded no further work was warranted for the purposes of VCCEP.

Several panelists commented favorably on the hazard assessment for MEK, stating the dataset was sufficient to address all life stages, and the discussion of toxicity endpoints was adequate. They agreed with using results from sBA toxicity tests to support the MEK dataset. One member commented that studies were not designed specifically to uncover hazards that might exist for children, but others noted the dataset contained no triggers suggesting child-specific testing was needed. Several panelists thought the RfD and RfC were overly conservative, with one member suggesting the RfC value might be increased as much as 30-fold. After further discussion of the existing toxicity data, the panel members found the hazard assessment to be satisfactory.

Many panelists said the exposure assessment was done well, and they favored the approach that was used. Some others were not satisfied with the assessment of exposures to prospective parents or fetuses. They said the submission contained all the required data, but not all the

calculations and evaluations were presented. One member remarked that not all the assumptions were sufficiently conservative. Most panel members agreed the exposure assessment could be improved by more clearly presenting the reasons why certain population groups were not individually assessed, but they concluded that the exposure assessment was sufficient for a Tier 1 assessment.

In discussing the risk assessment, two panelists applauded the annualized aggregations of chronic exposures, but noted that potential short-term exposures were not aggregated for all target populations. Other members found the risk assessment to be more conservative than necessary, especially when calculating safety margins for the younger age groups. Several panelists said the clarity of the risk assessment could be improved by showing comparisons among the broad types of exposure sources and by providing more explanation of how the hazard and exposure data were combined to characterize the risk for each target population.

In summary, panel members concluded that the MEK database and submission were adequate, and the key areas of hazard, exposure, and risk were sufficient to characterize risks to children for the purposes of the VCCEP program. Some panelists were highly complimentary of the submission and said the risk assessment was more conservative than necessary. Others thought data gaps existed related to risks to prospective parents and fetuses. Some suggested additional analyses might be conducted on the existing data to better characterize exposure and risk in some areas. A number of panelists noted a lack of clarity in some sections of the submission, saying the manner of presentation caused difficulty in understanding how risk was characterized for some age groups. None of the panelists thought these issues should be classified as data needs. No data needs for MEK were identified by any of the panel members.

1. Participants

1.1. Sponsor

VCCEP Task Group of the American Chemistry Council Ketones Panel

1.2. Presenters

Laura H. Keller, Ph.D. Toxicology
Product Stewardship/Regulatory Affairs Coordinator
ExxonMobil Chemical Company

Kenneth Pavkov, Ph.D. Anatomy
Advanced Toxicology Associate
ExxonMobil Biomedical Services, Inc.

Rosemary T. Zaleski, M.S. Environmental Sciences
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1.3. Peer Consultation Panel Members

John Balbus, M.D., M.P.H.
Environmental Defense

James V. Bruckner, Ph.D. Toxicology
University of Georgia

George P. Daston, Ph.D. Developmental Biology and Teratology
The Procter & Gamble Company

Michael L. Dourson, Ph.D. Toxicology, DABT
Toxicology Excellence for Risk Assessment (*TERA*)
(Panel Chair)

Elaine A. Cohen Hubal, Ph.D. Chemical Engineering
U.S. EPA, National Exposure Research Laboratory

Michael Jayjock, Ph.D. Environmental Engineering
The LifeLine Group

Sam Kacew, Ph.D. Pharmacology
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Jennifer Seed, Ph.D. Developmental and Cellular Biology
U.S. EPA, Risk Assessment Division

Chad Sandusky, Ph.D. Pharmacology
Physicians Committee for Responsible Medicine

Kimberly M. Thompson, Sc.D. Environmental Health
Harvard University

Susan Hunter Youngren, Ph.D. Environmental Biology and Public Policy
Bergeson & Campbell, PC

1.4. Observers and Other Attendees

A list of observers and other attendees is found in Appendix A.

2. Background

This peer consultation meeting has been organized by Toxicology Excellence for Risk Assessment (*TERA)*. *TERA* is an independent non-profit organization with a mission to protect public health through the best use of toxicity and exposure information in the development of human health risk assessments. *TERA* has organized and conducted peer review and peer consultation meetings for private and public sponsors since 1996. Under this program, *TERA* is organizing peer consultation meetings for assessments developed as a part of the Voluntary Children's Chemical Evaluation Program (VCCEP). The MEK assessment was submitted by the VCCEP Task Group of the American Chemistry Council Ketones Panel (ACCKP). ACCKP consists of the following companies: Celanese, E. I. duPont de Nemours & Company, ExxonMobil Chemical Company, and Shell Chemical LP. The consultant to ACCKP on exposure issues was ExxonMobil Biomedical Sciences, Inc.

The VCCEP program is a voluntary pilot program and part of the U.S. Environmental Protection Agency's (EPA) Chemical Right-to-Know Initiative (http://www.epa.gov/chemrtk/vccep/childhlt.htm). The goal of VCCEP is to enable the public to better understand the potential health risk to children associated with certain chemical exposures. The key question of the program is whether the potential hazards, exposures, and risks to children have been adequately characterized, and, if not, what additional data are necessary. The EPA has asked companies that manufacture and/or import 23 chemicals (that have been found in human tissues and the environment in various monitoring programs) to volunteer to sponsor chemical evaluations in a pilot program. Sponsorship requires the companies to collect or develop health effects and exposure information on their chemicals and then to integrate that information in a risk assessment and a data needs assessment.

The VCCEP pilot program was designed to use a tiered testing approach. For toxicity data, specific types of studies have been assigned to one of three tiers. For exposure data, the depth of exposure information increases with each tier. Tier 1 assessments should use all available data,

and therefore some of the Tier 1 chemical assessments will include more than what is indicated for Tier 1. ACCKP volunteered to sponsor a Tier 1 assessment for MEK, utilizing the available information and data (links to the submission document and appendices are available to the public on the Internet at http://www.tera.org/peer/vccep/MEK/MEKwelcome.html). If data needs are identified through this process, ACCKP will choose whether or not to volunteer for any additional data generation or testing and whether to provide a Tier 2 assessment.

To provide wide-ranging scientific review of the sponsor's assessment, each submission undergoes review and discussion by a peer consultation panel in an open meeting where the public is invited to observe. The purpose of the meeting is to provide a science-based peer consultation on the data needs for the chemical, utilizing the assessment submitted by the sponsor, as well as the expertise and knowledge of the panel.

The VCCEP Peer Consultation Panel for MEK consisted of 11 members independently selected by *TERA*. Each panel member disclosed information regarding potential conflicts of interest and biases for the VCCEP program in general and for MEK in particular. *TERA* evaluated these disclosures in selecting the panel members. The disclosures were publicly presented at the beginning of the meeting (see Appendix B for the panelist disclosure statements). The panel members have experience in various disciplines, including toxicity testing, exposure evaluation, risk assessment, and children's health. The panel received a copy of the submission and key references approximately one month before the meeting, so that they had adequate time to review the documents and prepare for the discussions. Panel members brought a range of views and perspectives to the peer consultations, reflecting the interest in VCCEP by a wide range of stakeholders. The panel did not attempt to reach consensus, rather the individual opinions of the members were noted.

Members of the public were invited to attend the peer consultation meeting to observe the panel discussions. They were also given the opportunity to provide brief oral and written technical comments on the assessment document for the panel's consideration.

TERA prepared this meeting report. It summarizes the sponsors' presentations, the panel discussions, the sponsors' comments, and any comments from the public. The meeting report is a summary, not a transcript. Individual opinions of the panel members are noted (although not identified by name), along with areas of agreement and disagreement. Panel members have reviewed and commented on the draft report. The sponsor was also given the opportunity to review the draft report to confirm the accuracy of the sponsor presentations and comments. Changes suggested by the panel members or sponsors were shared with the full panel before the report was finalized. *TERA* staff resolved any differences of opinion by reviewing materials from the meeting. This report is made available to the public on the Internet at http://www.tera.org/peer/vccep/MEK/MEKwelcome.html.

This report is organized into sections corresponding to the submission's hazard assessment, exposure assessment, and risk characterization/data needs sections. Issues and concerns raised during the panel discussions do not necessarily lead to recommendations for additional studies or data compilations. The recommendations of the panel members regarding the need, or lack of need, for additional data apply only to the VCCEP program.

3. Introductions, Conflict of Interest, and Meeting Process

The meeting opened with a welcome by Ms. Jacqueline Patterson of *TERA*. She described the background and purpose of the VCCEP and the agenda for the meeting. Ms. Patterson noted that copies of panel members' biosketches and conflict of interest (COI) and bias disclosure statements were provided to all attendees (see Appendix B). All the panel members introduced themselves and noted whether they had additions or changes in their disclosure statements. No members had any additions or changes. No written comments on MEK were received from the public.

Dr. Dourson, the panel chair, described how the meeting would be run. He explained that discussions would be based on the items found in the Charge to the Panel (located in Appendix B). He noted that all panelists would have the opportunity to state their own positions on the charge items and to ask one another clarifying questions and further discuss the issues. No attempt would be made to reach consensus positions on the charge items. The chair reminded the panel that the purpose of the peer consultation is not to critique the submission document *per se*, but rather to evaluate the adequacy of the data for characterizing risk to children.

This report on the MEK peer consultation meeting is organized into three sections: hazard assessment, exposure assessment, and risk characterization and data needs.

4. Hazard Assessment

4.1. Sponsor Presentation

Dr. Kenneth Pavkov, an Advanced Toxicology Associate with ExxonMobil Biomedical Services, Inc., summarized the hazard assessment data presented in the sponsor's submission (see Appendix D for the presentation slides). He noted that studies conducted on MEK (or on its immediate precursor, secondary butyl alcohol [sBA], which is extensively metabolized to MEK) fulfill most of the hazard requirements listed in the VCCEP Tiers. Results of these studies were sufficient to allow EPA to develop an IRIS (Integrated Risk Information System) RfC (5.0 mg/m^3) and RfD (0.6 mg/kg-day) in 2003 (U.S. EPA, 2003).

Dr Pavkov briefly described each study, tier by tier. The Tier 1 results demonstrated MEK's low order of acute toxicity and lack of genotoxicity. The Tier 2 studies showed MEK and sBA metabolism, providing pharmacokinetic data to support the use of sBA as an MEK surrogate. Other Tier 2 studies were conducted to assess subchronic toxicity, neurotoxicity, reproductive and developmental effects, and immunotoxicity. These tests included a 2-generation rat oral reproduction study with sBA (Cox et al., 1975) that served as the basis for the IRIS RfD of 0.6 mg/kg-day, and a mouse inhalation developmental toxicity study with MEK (Schwetz et al., 1991) used to derive the IRIS RfC of 5.0 mg/m^3. The critical effect for the RfD was decreased pup body weight, and the critical effect for the RfC was skeletal variations. MEK showed no indication of immune suppression or enhancement in a 90-day study that included extensive histopathology of lymphatic tissues (Cavender et al., 1983). These data, together with the

structure activity relationship existing between MEK and acetone, support the conclusion that no further immunotoxicity testing on MEK is required.

Dr. Pavkov explained that the sponsors do not believe Tier 3 studies on MEK are required for the following reasons: (1) chronic toxicity/carcinogenicity testing is not required because MEK is not genotoxic and SAR (structure activity relationship) analyses suggest the chemical is unlikely to be carcinogenic based on the absence of any structural alerts indicative of carcinogenic potential. The IRIS toxicology review and the Screening Information Assessment Report on MEK (U.S. EPA, 2003) reached the same conclusion; (2) a neurotoxicity screening battery is not required because results of the existing animal studies provide no convincing evidence that exposure to MEK alone produces persistent neurotoxic effects. This is the conclusion of the IRIS toxicology review on MEK; in addition, EPA has excluded MEK from it neurotoxicity test rule; (3) developmental neurotoxicity testing is not required because the totality of scientific evidence for MEK (fetal histopathology from multiple developmental studies, pup evaluation from a 2-generation reproduction study, and histopathology and clinical observations from 3 and 6 month subchronic studies) is not suggestive of a developmental toxicity hazard.

In conclusion, Dr. Pavkov noted that the available studies on MEK and sBA indicate MEK has a low order of toxicity, and the results support the conclusion that there are no data needs for the hazard assessment.

4.1.1. Clarifying Questions from Panel

In reply to a panelist's questions about MEK possibly producing enzyme induction, saturating metabolic pathways, or having an increased toxicity potential in people with liver disease, the sponsor responded that increased liver weights observed in some animal studies indicated enzyme induction occurred. Metabolism studies did not suggest any MEK accumulation or saturation of metabolic pathways. Literature searches of populations with liver disease (e.g., jaundiced children) showed nothing to indicate MEK would be more toxic in people with compromised liver function. In addition, MEK is eliminated via exhalation from the lungs. This route of elimination would continue to occur in the presence of any liver dysfunction. A panelist cautioned that MEK's ability to induce cytochrome P450 might be toxicologically significant. Although these changes are adaptive to MEK, they can potentiate toxicity of other chemicals that undergo metabolic activation (e.g., *n*-hexane, methyl-*n*-butyl ketone, and 2,5-hexanedione); he cited the report by Traiger et al. (1989) showing mixed-function oxidase induction can potentiate toxicity of chemicals that undergo metabolic activation. However, this panel member thought the low levels of MEK to which children are likely to be exposed are probably too low to exert this action.

Referring to data from the Cox et al. (1975) study on page 30 of the submission, two panelists asked for clarification of the dam and pup high dose levels and the NOEL (No Observed Effect Level) and NOAEL (No Observed Adverse Effect Level) values. The sponsor replied that the 3% sBA solution given to the F_0 generation caused observable toxicity, so the concentration was reduced to 2% for the F_1 generation. The NOAEL value of 1771 mg/kg-day (1% sBA) was correct for both the dams (F_0) and the pups (F_1). This study was a combined 2-generation reproductive toxicity and prenatal developmental study. The F1 generation animals were reared

to maturity and mated to produce an F_2 generation. A panelist remarked that this study was unusual because of the large number of pups that were examined. He thought the extensive evaluations conducted on young animals should be emphasized in the submission because the study was more thorough in this regard than is normally seen.

Noting that the Cox et al. (1975) used sBA as the test material, a panel member asked if the sponsors were confident the study provided sufficient information of what would be seen with MEK. The sponsors said they were confident because metabolism studies showed 96% of sBA is rapidly converted to MEK; therefore the high doses of sBA in the Cox study produced high doses of MEK in the test animals. Another panelist cautioned that using the 96% figure for conversion of sBA to MEK in the Cox study is an over-simplification because a multi-generation study, such as this, would have complicated enzyme kinetics with some enzyme pathways likely to be saturated. He suggested that the effects seen in the Cox study were likely to be from a combination of sBA and MEK.

4.2. Panel Discussion of the Hazard Assessment

The panel discussion on Hazard Assessment addressed the following items from the Charge to the panel:

- Discuss whether the information available on mode of action, toxicity studies, and ADME (absorption, distribution, metabolism, and elimination) is adequate to identify and assess potential hazards a) to prospective parents, b) *in utero*, and c) to the infant and child.

- Discuss whether the quantitative hazard and dose-response information (e.g., RfD, RfC) is appropriately chosen or developed.

The panel addressed these two charge items through discussions of the topics presented below.

4.2.1. Adequacy of the Toxicity Database

In considering database adequacy, several panelists said MEK had a robust dataset that was sufficient to address all life stages, and they found the hazard assessment's discussion of relevant toxicity endpoints to be adequate. They said using the results from toxicity studies conducted on sBA to support and supplement the MEK dataset was appropriate, and they saw no significant data gaps in the hazard assessment. One member said the mode of action was not defined, but MEK did not appear to have much toxicity.

Another panelist said, although the test results in the MEK dataset raised no red flags for him, the database overall was not designed to uncover hazards that might exist specifically for children. He believed more focused tests should have been conducted to provide results with

more direct childhood relevance[1]. He noted the database lacked studies with sensitive endpoints in which animals were exposed to MEK during their periods of greatest vulnerability. For example, the data provided by studies of adult rats indicated a lack of neurotoxicity in adults, but animals were not exposed during neurogenesis *in utero* or postnatally, which are the periods of maximum susceptibility. As a second example, he thought it was unlikely that Cox et al. (1975) had looked for adverse effects on the visual, auditory, or endocrine systems in the second generation of rats that ingested sBA. Several other panel members expressed a different point of view, saying the existing data set on MEK toxicity contained no triggers to suggest more child-specific testing was needed. One member explained that the toxicity database on MEK includes older studies that were not conducted expressly for MEK's evaluation in the VCCEP or for the evaluation of children. Rather, the studies were conducted to generate a general toxicity profile that could be applied to human risk assessments for all age groups. She said this is the reason the MEK studies and testing parameters did not focus on children. However, in spite of the general nature of the MEK toxicity profile, this panelist thought the existing dataset contained testing at sufficiently high dose levels and with enough multiple studies evaluating key endpoints (e.g., four studies were conducted on developmental toxicity) to enable the information to be used for assessing the potential hazards to children (including the fetus, neonate, and adolescent). Other panel members acknowledged the possibility that MEK might have unknown toxicities that could be revealed by more sensitive, child-specific test methods (and they noted such new testing strategies are being developed by the National Academy of Sciences and other groups). The majority of panel members concluded that no further toxicity testing on MEK was indicated and that the available toxicity database was sufficient.

4.3. Quantitative Hazard and Dose-Response Benchmarks

One panel member considered the EPA's IRIS RfD (0.6 mg/kg-day) and RfC (5 mg/m^3) to be extremely conservative values. He said the doses of MEK received by the adult rats in the key developmental studies likely were high enough to cause CNS depression that would result in decreased food intake. He thought the observed toxic endpoints in the studies (i.e., decreased body weight and delayed skeletal ossification in offspring) probably were due to diminished maternal food consumption. Because of this, he thought that the uncertainty factors of 1,000 and 300 used to derive the IRIS RfD and RfC were excessive. Other members agreed, saying the IRIS RfC used uncertainty factors that went beyond those needed for developmental effects, and it was overly conservative as an RfC for developmental toxicity. One member thought it would be justifiable to adjust the IRIS RfC upward. He noted the RfC included a 10-fold uncertainty factor for database insufficiency and an adjustment of approximately 3-fold because the exposure to the animals was less than 24 hours/day. Regarding the database insufficiency factor, he said while it may be argued that there are gaps in the *overall* database, this does not include the *developmental toxicity* database in which two species were tested by the relevant route. The results of those studies are supported by oral studies and by studies on sBA. Therefore, if the

[1] After the meeting, this panelist explained that his comments were not intended to be a criticism of this particular document because he does not see a cause for concern about MEK. Rather, he believes EPA should provide guidance to sponsors requesting them to address child-specific pharmacokinetic (i.e., absorption, distribution, metabolism, and elimination) and pharmacodynamic (e.g., windows of vulnerability in susceptible organ systems) factors. These factors may not always apply to the VCCEP chemical under review, but they should always be considered and experimental evidence and/or logic presented for why they do or do not apply.

RfC were based on developmental toxicity, the 10-fold factor for data insufficiency would be unwarranted. In addition, if the RfC were used in comparisons to exposures of 7 hours/day or less, the 3 fold duration-of-exposure adjustment also would be unwarranted. He concluded that the most appropriate point of comparison for single, short-term (less than 7 hours) exposures would be an RfC based on developmental toxicity. Such an RfC could be 30-fold higher than the current IRIS RfC, which is intended to protect against lifetime daily exposure. Several other members agreed that using an RfC based on the NOAEL from the developmental studies would be an appropriate point of comparison for certain (e.g., acute) human exposure scenarios. One member suggested that uncertainty factors to account for chronic exposures might not be needed because of MEK's rapid metabolism and clearance.

After discussing the above topics related to the sponsors' hazard assessment, most panel members confirmed their satisfaction with the existing toxicity data.

5. Exposure Assessment

5.1. Sponsor Presentation

Ms. Rosemary Zaleski, an exposure consultant from ExxonMobil Biomedical Services, Inc., summarized the exposure data presented in the sponsor's written assessment (see Appendix D for the presentation slides and also for the table ["Estimated MEK Air Concentrations for the Exposure Event, Active Use Scenarios"] that was distributed to the panel and observers to supplement her slide presentation). Ms. Zaleski noted that excessive use or misuse situations were not addressed in the exposure assessment; however, she thought such situations were infrequent because of MEK's sensory irritation potential and strong odor, plus the fact that MEK-containing products are labeled with warning statements to discourage excessive use or intentional misuse.

MEK is a mammalian metabolite, is present in all food groups, and is produced by microbes, algae, plants, and other organisms. Its primary use is industrial, but it also is an ingredient in consumer products, especially coatings and adhesives. The exposure assessment compiled information on all known sources of MEK and identified those pathways relevant to children's exposure. Results indicated that, on a chronic basis, food is the main exposure source (0.1 – 0.3 mg/kg-day) for the general population of children, including the nursing infants of mothers who are not occupationally exposed. Ambient media concentrations were generally low, often below detection limits. Indoor uses of various consumer products resulted in higher acute exposures, but these were short-lived. MEK is rapidly metabolized and is excreted in the urine and also eliminated via exhalation from the lungs, so acute exposures do not lead to cumulative increases in body burdens.

None of the consumer products containing MEK were targeted specifically towards children, with the exception of hobby model paints and adhesives targeted towards older children and adults. Integrated data from consumer product databases, Material Safety Data Sheets, and store visits identified the consumer products with the greatest exposure potentials, and these were quantitatively evaluated for both inhalation and dermal exposures.

Child exposure was estimated for six age groups using assumptions intended to overestimate exposure. The range of exposures predicted for individual consumer products across all age groups were: 4 hour TWA: 0.03 - 92 mg/m^3; day of use dose: 0.0002 - 1.62 mg/kg-day; chronic dose: 0.00002 - 0.016 mg/kg-day (based upon median use exposure estimates, 90th percentile frequency of use each year, all use occurring indoors, and MEK being in all products at every use).

The only MEK exposure pathway unique to children was ingestion of breast milk. In the general population, infant exposure from breast milk ingestion ranged from an average of 0.0007 mg/kg-day to a high end of 0.0024 mg/kg-day (95th percentile estimated milk concentration, maximum milk intake). For nursing infants of occupationally exposed mothers, breast milk was the most significant exposure pathway. Based on the work of Fisher et al. (1997), the sponsors calculated that the bounding estimate for this exposure would be an average annual daily dose of 0.6 mg/kg-day. Because the conditions used in this bounding estimate (described in Section 8.6.2 on page 69 of the submission document) included several unrealistically conservative assumptions, the sponsors emphasized that a dose of this magnitude is not expected to ever occur. A more realistic high-end estimate for infant exposure from an occupationally exposed mother is 0.16 mg/kg-day.

5.1.1. Clarifying Questions from Panel

A panelist asked the difference in meaning between the terms "bounding estimate" and "high-end exposure." The sponsor responded that, as they were using these terms, a bounding estimate was a calculated value intended to be greater than any worst-case dose expected to occur, while a high-end exposure was an estimate or measurement of the greatest exposure that was likely to occur. Another panel member noted that her understanding of the usual definition of a bounding estimate was different from the sponsors. She said worst-case exposures could be as high as a bounding estimate, but not higher. Therefore, she thought that, as commonly used, the terms bounding estimate and high-end exposure really meant the same thing. The sponsor replied that, in the case of MEK doses to infants from ingesting breast milk of working mothers, the 0.6 mg/kg-day value that was termed the bounding estimate was far above any dose expected to occur.

In response to a panelist questioning why the exposure assessment did not include a more thorough evaluation of prospective parents as a target population, the sponsor explained this was not considered necessary because the reproduction studies in the toxicity database did not indicate any specific effects for this population; however, prospective parents are addressed in more detail in the risk assessment.

Several panel members requested clarification of the way exposures had been aggregated and annualized, the sources of the data, whether the children's age-range exposure values were averaged from individuals or were group values obtained from published compilations, and how individual values in some of the tables (e.g., Table G 3.12) were obtained. The sponsors provided further details of their assumptions and calculations, clarifying that the exposure values were calculated using age-specific food intake rates. Exposure estimates were provided as one-

day intakes (people who ate the foods on that day) and annual average daily intakes (considers that not all food items are eaten every day). Child intake rates for specific food items were taken from U.S. Department of Agriculture 1999 (these data are also cited in U.S. EPA 2002), and child intake rates for broad food categories were taken from U.S. EPA 2002. Values for daily aggregate exposures (e.g., eating yogurt plus using an MEK-containing solvent to clean a paint brush) were not provided, but such values could be calculated from the data compiled in the appendices.

Asked if they compared the magnitude of exposures from industrial, ambient, and endogenous sources, and whether they had compiled medical data on children who had abused MEK-containing products (e.g., sniffing model airplane glue), the sponsors said they had not compared the magnitude of exposures from different sources. Such comparisons would not be accurate because quantitative data on food content, endogenous production, and other sources is lacking. Medical data from product abuse situations was not compiled because any adverse effects seen from the products would almost certainly have been caused by non-MEK components of the products. The sponsors explained that MEK is among the least toxic ingredients in the types of products that are most subject to intentional misuse.

5.2. Panel Discussion of the Exposure Assessment

The panel discussion of the exposure assessment addressed four charge items:

- Discuss whether the fate of this chemical is adequately understood.
- Based on the information at hand, discuss whether the available data are adequate to characterize exposure to children and prospective parents, taking into consideration the conditions of exposure (sources, routes, frequency, duration, intensity, etc.).
- Discuss whether all time periods relevant to childhood exposure [(a) parental exposure prior to conception, (b) prenatal development, (c) and postnatal development to the age of sexual maturation] have been adequately considered.
- Discuss whether the estimates of exposure have been calculated appropriately and correctly.

The panel addressed these charge items through discussions of the topics presented below.

5.2.1. Adequacy of the Exposure Assessment

Many panel members commented favorably on the MEK exposure work, with one member saying it was the most complete she had ever seen. The majority of panelists agreed that the fate of MEK was adequately understood, and they noted its rapid metabolism and degradation in the body and in the environment is well documented. Several members thought the exposure assessment for children was done well, with one member saying she was pleased to see that the appropriate uncertainties were presented for several of the estimates, and another adding that a good job was done in dividing the children into reasonable age brackets.

Some of the panelists were not satisfied with the exposure assessment of prospective parents. One member remarked that not all the assumptions for exposure situations were sufficiently conservative. In some cases, she found that adjustments had been made to reduce published exposure values. As an example, in Section 8.6.2 (page 69) of the submission, the infant milk ingestion value of 920 ml/day assumed by Fisher et al. (1997) was scaled down to 688 ml/day to agree with the average annual daily intake reported in the EPA Child Specific Exposure Factors Handbook (U.S.EPA, 2002). She suggested that it would have been preferable to show all the values as a range, rather than scaling back the Fisher value. Another member added that MEK occurs in nursing mothers' exhaled air, as well as in their breast milk. Two members noted that although occupationally exposed nursing mothers had been discussed, an exposure assessment was not presented for pregnant women, whether occupationally exposed or not. They thought all the data needed for assessing exposures of pregnant women were included in the submission, but the calculations and evaluations had not been done. The sponsor acknowledged that the assessment did not present the rationale why pregnant women or prospective parents in general were not considered specific target classes, and further explained that the lack of toxic effects in reproduction studies indicated these target classes had no special vulnerabilities warranting separate exposure assessments. A member of the panel agreed, adding that exposure assessments should not be done in a vacuum. He believed it was appropriate to consider the results of the hazard assessment, as the sponsors had done. While this panelist saw no deficiencies in MEK's exposure assessment, he suggested the assessment would be improved by more clearly presenting the reasons why certain population groups (e.g., prospective parents) were not individually assessed.

5.2.2. Evaporation of MEK

One panel member alerted the panel and sponsors to an issue with the evaporation rate of MEK that was used in some calculations in the exposure assessment. He explained that the calculation establishing the vaporization rate, which was presented in Appendix G-6 of the submission, uses a mass transfer coefficient no longer used by EPA. Use of a more appropriate evaporation rate would result in higher inhalation exposures, but lower dermal exposures. The sponsor noted that the out-dated evaporation rate was used in only one exposure scenario, which involved an open can of paint. She said that using the higher evaporation rate in this scenario would not have any meaningful effect on the overall exposure assessment. The panel member agreed with the sponsor's conclusion. Other members also agreed, but recommended that a spreadsheet containing the more appropriate evaporation rate be included as an appendix to the MEK meeting report, along with a more detailed explanation by the panel member. (Appendix E contains this spreadsheet and further explanation.)

After discussing the above topics related to the sponsors' exposure assessment, the majority of panel members concluded that the assessment was sufficient for a VCCEP Tier 1 assessment.

6. Risk Characterization and Data Needs

6.1. Sponsor Presentation

Dr. Laura Keller, Product Stewardship/Regulatory Affairs Coordinator for ExxonMobil Chemical Company, summarized MEK's risk characterization and data needs (see Appendix D for the presentation slides). She reviewed the calculations comparing chronic exposure data from aggregated exposure scenarios for all age groups to the U.S. EPA IRIS RfC and RfD values. The 16-19 year old age group had the highest aggregate value for active exposure: 0.035 mg/kg-day, providing a MOS[2] of 17. The <1 year old age group had the highest aggregate value for passive exposure: 0.027 mg/kg-day, providing a MOS of 22. Dr. Keller noted the scenario of a maximally exposed mother nursing an infant at work throughout the day provided a realistic worst-case exposure estimate for the infant of 0.16 mg/kg-day (MOS of 4). She explained that adding the aggregate chronic value for infants (0.027 mg/kg-day) to this breast milk ingestion value did not substantially change the risk assessment, as the total (0.19 mg/kg-day) resulted in a MOS of 3. Dr. Keller compared the acute MEK exposure data to the threshold for sensory irritation (200 ppm; 590 mg/m^3) and to acute exposure benchmarks based on the NOAEL for developmental effects (50 mg/m^3 for 24-hour exposures; 171 mg/m^3 for exposures of 7 hours or less). In all instances these comparisons resulted in MOS values greater than 1.

Dr. Keller concluded that the quantitative risk characterization indicates children's exposure to MEK poses negligible health risks. Short-term air concentrations are not expected to cause adverse effects, and the potential for aggregate chronic exposures to reach levels of concern is considered low. The sponsors believe the MOS values presented in this risk assessment are more likely to be understated than overstated. On this basis, they conclude no further studies, exposure measurements, or risk analyses on MEK are warranted for the purposes of VCCEP.

6.1.1. Clarifying Questions and Comments from the Panel

One member asked if the assessment of potential aggregate exposures (slides 8 and 9 in the sponsor's risk assessment presentation) assumed maximum concentrations of MEK in the products. The sponsor confirmed that maximum concentrations had been assumed. Acute exposures were estimated using maximum concentrations for all scenarios. In addition, median concentrations were used for several scenarios. As discussed in the exposure presentation, chronic exposures were estimated based upon median use per event when estimated (otherwise, the maximum use value per event was used), 90th percentile frequency of use each year, all use occurring indoors, and MEK being in all products at every use. The chronic estimates were used in the aggregate assessment. For many scenarios, maximum MEK concentrations were used in the chronic exposure estimates. Three scenarios represented greater than 90% of the aggregate exposure estimate. In two of these scenarios (aerosol wood stain and pure MEK evaporation during brush cleaning), the maximum MEK concentration was used. In the third scenario (spray paint use), an MEK concentration of 0.10 was used as compared to a maximum concentration of 0.13. The selection of the median use per event, coupled with a 90th percentile use frequency for

[2] MOS (Margin of Safety) is defined as the RfC or RfD divided by the exposure of interest, when both are expressed in the same units.

developing a chronic estimate, was based upon the approach taken in the U.S. EPA's E-FAST Model.

In response to another panelist, the sponsor said the uncertainty factor for data insufficiency used in the IRIS RfC was added to account for the lack of a chronic study.

6.2. Panel Discussion of the Risk Characterization

The panel discussion on the risk characterization addressed the following charge item:

- Discuss whether the Risk Characterization appropriately integrates the exposure and hazard information for this chemical and adequately characterizes the risk a) to prospective parents, b) *in utero*, and c) to the infant and child.

One panelist complimented the sponsors on the risk assessment, saying it was exhaustive, compelling, and more conservative than necessary. Other members echoed these favorable comments. Another member said the risk assessment failed to sufficiently address the unique, potential vulnerabilities to MEK that might exist in infants and children. As an example, he noted that the only child-specific factor taken into account when calculating the inhaled dose was inhalation rate (in Appendix G-14). He thought additional determinants known to be important in calculating the systemic uptake of volatile solvents should have been evaluated specifically for children, such as cardiac output and pulmonary perfusion rate. He also thought the assessment should have considered MEK's metabolism parameters in the incompletely developed enzyme systems of the fetus and neonate. He cited the report by Smyth et al. (1962) showing oral LD_{50} values for newborn animals to be a small fraction of adult values, and noted that diminished oxidative and conjugative metabolic capacities in the neonates were likely responsible for this finding. He said factors such as these may or may not be cause for concern with MEK, but they should have been addressed.

Another panel member observed that the risk assessment for acute exposures to prospective mothers appeared to consider only exposures from use of consumer products. The sponsor replied that other exposure sources, such as air and food, did not make meaningful contributions to acute exposure scenarios, so they were discussed only in the context of the chronic risk assessment. The panel member agreed with the sponsor that the proper place for discussion of these other sources was in the chronic risk assessment, but she said that mentioning them also in the acute risk assessment would have helped demonstrate the completeness of this assessment. This same panelist, referring to Table 9-1 (page 111) in the submission, found that the sponsors were more conservative than necessary in calculating the MOS values for the younger age groups (<1 year and 1-2 years). She explained that instead of comparing the exposures of these age groups to the IRIS RfD, which was based on adverse reproductive effects and included an uncertainty factor to account for the lack of a chronic study in the database, the comparison could have been made to adverse health effects benchmarks based on shorter-term studies with toxicity endpoints more relevant to the young age groups. She suggested the submission might point out the high degree of conservatism used in the risk assessment of these age groups.

Three panelists said the clarity of the risk assessment would be improved if comparisons were made among the broad types of exposure sources: foods, ambient environment, consumer product use, and occupational. The sponsors responded that all of the data needed to make these comparisons were included in the submission, and such comparisons could be done. The three panelists replied that doing this work would strengthen the risk assessment overall, and they suggested the comparisons be made. Several other members found the aggregate exposures and the MOS values to be both reasonable and conservative. A member added that the aggregated exposures were overly conservative because it was not plausible that a single person would be able to experience all of the different exposures assumed to occur within the short time frame that MEK exists in the body before it is metabolized. Another panelist, citing a report on MEK kinetics in humans (Liira et al., 1988), noted that that MEK can persist in the body for 12 to 24 hours.

One panelist commended the sponsors for the manner in which they presented the risk assessment for short-term exposures. He especially liked their use of alternative exposure benchmarks for 7 and 24 hour time periods (slides 10 and 11 in the sponsor risk assessment presentation, Appendix D). However, he recommended the sponsors not accept and use the IRIS RfC/RfD values in some situations and then claim they are too conservative for other situations. He suggested it would be preferable to say the degree of uncertainty associated with the basis of the RfC/RfD values may differ, depending on the risk assessment situations to which they are applied. In situations where the degrees of uncertainty are diminished, the derivation and use of less conservative RfD/RfC values may be justified.

6.3. Panel Discussion of Data Needs

The panel discussion of Data Needs addressed two charge items:

- Identify any additional hazard information that is needed and discuss why it is necessary. The focus should be on those studies listed in the next VCCEP tier.

- Identify any additional exposure data and analyses that are needed and discuss why this information is necessary.

The Panel Chair reviewed the definitions of *data gaps* and *data needs:* in the context of the VCCEP *data gaps* are any areas in which information is lacking, and *data needs* are those data gaps for which additional information is required before the potential risk to children can be adequately characterized. He then asked each panel member to identify and discuss any data gaps or data needs he or she saw in the hazard, exposure, or risk assessments.

None of the panelists thought that further data or analyses were needed to characterize MEK's risks to children for the purposes of the VCCEP program. However, some members of the panel identified items they considered data gaps or issues related to clarity in the hazard, exposure, or risk assessment presentations. Some members said the exposure of prospective parents could be addressed more specifically, and estimating fetal exposure of occupationally exposed women should be considered (perhaps via measurement of placental transfer or similar techniques). Other members thought measurement studies were unnecessary in light of the information

available from animal reproduction and developmental studies, and also from pharmacokinetics. Two panelists identified the developmental neurotoxicity test as a data gap, but not a data need.

Most panelists agreed the assessment included the necessary data, but several thought further analyses of these data could be presented to demonstrate more clearly what the potential risks to children might be. One member recommended that in addition to aggregating exposures on an annual basis, the authors should present daily exposure aggregates as well. These could consist of reasonable assumptions of high-end ambient levels, combined with the consumption of high-end foods within a few hours of using a limited number of high-end MEK consumer products. Another member suggested that broadly comparing the general sources of MEK exposure (foods, consumer products, ambient environment, and occupational situations) would make it easier to understand their relative importance.

A number of panelists remarked that the submission lacked clarity in some areas, noting that the data are included in the document, but further analysis should be done and presented to the reader. They suggested the clarity could be improved by better explanations of how and why the chronic and short-term health effects benchmarks were selected and why the selected benchmark is appropriate for the particular exposure scenario. Panel members also thought the presentation could be improved by further explanation of how the health benchmarks and exposure data were integrated to characterize the risk to prospective parents, to the fetus *in utero*, and to the infant and child.

In summary, most panel members concluded the dataset compiled on MEK was adequate, and the key areas of hazard, exposure, and risk were sufficient to characterize risks to children for the purposes of the VCCEP program. Some panelists identified data gaps related to estimating risk to fetuses. Others suggested additional analyses could be conducted on the existing data to better characterize the exposure and risk. Several panelists expressed concern about a lack of clarity in some sections of the submission. They thought the manner of presentation sometimes made it difficult to understand how the risk was characterized for some populations and age groups. None of the panelists thought that any of the issues they raised should be classified as data needs. No data needs for MEK were identified by any of the panel members.

7. References

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